Statistical Analysis Plan
for the
NSAIDs in Sciatica (NIS) Trial

An investigator-initiated randomized placebo controlled trial of Naproxen

in patients with sciatica

Version1
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ABBREVIATIONS

ARR	Absolute Risk Reduction
CI	Confidence Interval
CRF	Case Report Form
CT	Computed Tomography
DDD	Defined Daily Dose
e-CRF	Electronic Case Report Form
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GAMM	Generalized Additive Mixed Model
GLMM	Generalized Linear Mixed Model
IQR	Inter Quartile Range
ITT	Intention-to-treat
LMM	Linear Mixed Effects Model
MAR	Missing At Random
MCAR	Missing Completely At Random
MI	Multiple Imputation
MME	Morphine Milligram Equivalents
MNAR	Missing Not At Random
MRI	Magnetic Resonance Imaging
NIS	NSAIDs In Sciatica
NNT	Numbers Needed to Treat
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PP	Per protocol
RCT	Randomized Controlled Trial
RR	Risk Ratio
RMDQ-S	Roland Morris Disability Questionnaire for Sciatica
SAP	Statistical Analysis Plan
SBI	Sciatica Bothersomeness Index
SD	Standard Deviation

AMINISTRATIVE INFORMATION

1 Title and trial registration

Title	NSAIDs in sciatica (NIS), an investigator initiated randomised placebo controlled trial of Naproxen.
EudraCT	2014-003623-21
ClinicalTrials.gov	NCT03347929

2 SAP version

SAP version	1
SAP date	21.11.21

3 Protocol version

Protocol ID no	SO-2017-1
Protocol version	2.4

4 SAP Revisions

SAP revision history	
Justification for each revision	
Timing of SAP revisions	

5 Roles of SAP contributers

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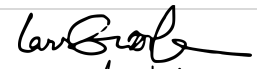
Person writing the SAP	Lars Grøvle	
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INTRODUCTION

7 Background and rationale

Sciatica is an established term for pain along the course of the sciatic nerve, radiating from the lower back or buttock into the leg. Sciatica is also known by terms such as low back-related leg pain, lumbosacral radicular syndrome or radiculopathy. Treatment of sciatica is primarily aimed at pain reduction, either by medication, or surgically by reducing pressure on the nerve root. Given their analgesic and anti-inflammatory mechanisms of action, non-steroidal anti-inflammatory drugs (NSAIDs) have been, and are still being regarded as standard therapy for sciatica. In a survey among American physicians 80% said they would recommend NSAIDs for initial management. In a study from general practice in Italy 90% of the sciatica patients had been prescribed an NSAID. In studies investigating the effect of surgery and manipulation, 50-60% of the patients were taking an NSAID at baseline (see protocol for references). However, the scientific evidence for this practice is generally lacking. Very few randomized controlled trials (RCT) of NSAIDs have been undertaken in patients with sciatica, and no study has shown clinically meaningful effects as compared to placebo.

NSAIDs involve the risk of serious gastrointestinal, vascular and renal side effects. Hence, there is a strong need to clarify their potential beneficial effects in sciatica. Naproxen, the active drug in this study, is a non-selective NSAID that has been in common use since 1976. Like other NSAIDs Naproxen provides analgesic, antipyretic and, in higher doses, anti-inflammatory effects. It is approved for the treatment of inflammatory rheumatic conditions, osteoarthritis, primary dysmenorrhea and musculoskeletal pain.

8 Specific objectives

8.1 Primary objective

To demonstrate that, in patients with sciatica, treatment with Naproxen 500 mg twice daily is superior to placebo for the improvement of leg pain intensity measured on a numeric rating scale (NRS) ranging from 0 to 10.

8.2 Secondary objectives

To demonstrate that, in patients with sciatica, treatment with Naproxen 500 mg twice daily is superior to placebo with respect to

- improvement in back pain intensity
- improvement in disability
- use of rescue medication
- global perceived change in sciatica/back problem
- improvement in sciatica symptom bothersomeness
- 30% and 50% improvement in leg pain
- concomitant use of opioid analgesics
- ability to work and study

STUDY METHODS

9 Trial Design

NIS is a multicenter, two-armed randomized, placebo controlled, double blind, parallel group, superiority phase IV trial.

10 Randomization

Study medicines will be packaged and labelled according to a pre-generated random number sequence; each sealed box will have a unique participant number. Computer-generated block randomization, stratified by center, will be used. Allocation to Naproxen or placebo will be at a 1:1 ratio.

11 Sample size

The sample size estimation is based on a minimum difference of interest between the Naproxen group and the placebo group of 1.5 at day 10. Assuming a standard deviation SD of 2.5 (see protocol for details and references), 90% power and a two-tailed 5% significance level, 60 subjects in each treatment arm is required. Allowing for a combined dropout and non-compliance rate ≤ 20% a sample size of 150 was determined.

12 Framework

Analyses will be within a superiority hypothesis testing framework, comparing Naproxen to placebo.

13 Interim analyses and stopping guidance

13.1 Treatment analyses

No interim treatment analyses will be performed.

13.2 Early stopping

The safety profile of Naproxen is well documented and established, and the dosing is under its approved label use. There is no reason to expect Naproxen to affect the rate of serious sciatica complications such as lower extremity paresis or cauda equina syndrome. As Naproxen is used under its approved label use no interim safety analyses will be conducted.

14 Timing of final analysis

All outcomes will be analyzed jointly after the end of the trial, i.e. after the last visit of the last subject, and data locking.

15 Timing of outcome assessments

Primary outcome: Leg pain (the primary outcome) is measured daily from baseline (day 0) to end of treatment (day 10).

Secondary outcomes

- Back pain is measured like leg pain
- Disability, assessed by the Roland Morris Disability Questionnaire for Sciatica (RMDQ-S), is measured at day 0, 5 and 10
- Rescue medication consumption is measured (i) at the end-of study-visit (by pill count) and (ii) daily from day 1 to day 10 (by self-report).
- Global perceived change is measured at day 5 and 10.
- Sciatica bothersomeness, assessed by the Sciatica Bothersomeness Index (SBI), is measured at day 0, 5 and 10.
- Concomitant use of opioid analgesics is assessed on day 0, 5 and 12 (±2).
- The ability to work or study is measured at day 0 and 10.

Table 1. Timing of outcome assessments

	Baseline	Start of treatment				End of treatment	End of study

Day	0	1	2-4	5 (±1)	6-9	10	12 (±2)
	Visit	Home	Home	Home	Home	Home	Visit
-Leg pain -Back pain	X	X	X	X	X	X	X
-SBI -RMDQ-S	X			X		X	X
Global perceived change				X		X	X
Work/study	X					X	X
Rescue medication (pill count)							X
Rescue medication (self-report)		X	X	X	X	X	
Opiod use	X			X			X

SBI Sciatica Bothersomeness Index, RMDQ-S Roland Morris Disability Questionnaire for Sciatica.

Visit windows.

Patient reported outcomes are captured using a web based real-time electronic diary (ViedocMe). The questionnaires are available 24 hours on the scheduled date. The end of study visit is scheduled on day 12 (±2).

STATISTICAL PRINCIPLES

16 Level of statistical significance

A two-tailed p value of less than 0.05 is considered to indicate statistical significance. We will report nominal p values.

17 Adjustment for multiplicity

We will not adjust for multiple comparisons. This trial has one primary outcome which will be analyzed in a single mixed-effect model and there are no planned subgroup analyses.

18 Confidence intervals

Parameter estimates will be reported with two-sided 95% confidence intervals (CI).

19 Adherence and protocol deviations

19.1 Adherence

The prescribed doses of study medication is one tablet twice daily for ten days, i.e. a total of 20 tablets. Adherence is assessed by the percentage of prescribed doses taken, measured by pill count if the bottle is returned. If the bottle is not

returned adherence will be based on self-report. Each day patients are asked to record study medication intake and give the reason if not taking the prescribed amount. Reasons for non-adherence will be reported based on patients' free-form text comments in the diaries, and investigators' comments in the case report forms (CRFs). This information will also be used in subsequent classification of potential missing data as being "missing not at random" (MNAR), "missing at random" (MAR) or "missing completely at random" (MCAR) [1].

19.2 Protocol deviations

Important (major) protocol deviations will be reported by the number of subjects who

- entered into the study not meeting the entry criteria
- developed withdrawal criteria during the study but were not withdrawn
- received the wrong study treatment or incorrect dose
- had less than 80% intervention adherence

Not important (minor) protocol deviations will be reported by the number of subjects who

- received drugs that they were encouraged to avoid during study, i.e. analgesics, NSAIDs, anti-depressants, tranquillizers, sleep medications, neuroleptics and anti-epileptic drugs, if not on a stable dose prior to enrollment.
- received drugs which would have excluded them from participating in the trial, i.e. anticoagulants, aspirin, serotonin reuptake inhibitors, systemic corticosteroids, diuretics, ACE-inhibitors and lithium.

20 Analysis populations

There will be 3 analysis populations:

1. The intention-to-treat (ITT) population, including all randomized subjects.
2. The per protocol (PP) population, including subjects without any important protocol deviations.
3. The safety population, including subjects who received at least one dose of study medication and who had at least one subsequent safety-related observation.

TRIAL POPULATION

21 Screening data

The population of interest is patients with severe sciatica who are referred to the participating centers, i.e. outpatient pain/back clinics at public hospitals in Norway. To enhance recruitment primary care clinicians are invited to refer eligible patients. A prescreening log will be established including information about age, sex and whether the eligibility criteria were fulfilled. Reasons why eligible subjects were not enrolled will be noted.

22 Eligibility

See trial protocol for inclusion and exclusion criteria.

23 Recruitment

We will present a CONSORT [2] diagram comprising the number of participants who were screened, eligible, randomized, receiving their allocated treatment, withdrawn and lost to follow-up.

24 Withdrawal and loss to follow-up

Reasons for withdrawal from the study will be coded as follows:

- Voluntary discontinuation by the patient
- Safety reason as judged by the principal investigator
- Important (major) protocol deviations
- Incorrect enrolment i.e. the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- A female patient becoming pregnant
- Patient's non-compliance to study treatment and/or procedures
- Death
- Other

Reasons for loss to follow-up will be provided if known. Depending on the data we will present the timing of withdrawal and loss to follow up in a Kaplan-Meier graph or incorporate it into the CONSORT flow diagram.

25 Baseline patient characteristics

Demographic and clinical characteristics will be summarised by assigned treatment group without comparisons, as shown in 32.1 (Planned table 1). Categorical variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator, which will be less than the number of patients assigned to the treatment group, will be reported either in the body or a footnote in the summary table. Continuous variables will be summarised by mean and standard deviation, or by medians and interquartile range (IQR).

ANALYSIS

26 Outcome definitions

26.1 Specification of outcomes.

The primary outcome is leg pain intensity (24 hours average), rated on a 0-10 NRS Higher scores indicate more severe pain.

Secondary outcomes:

- Back pain intensity (24 hours average), rated on a 0-10 NRS.
- Disability, measured by RMDQ-S (0-23), higher scores indicate worse disability.
- Sciatica bothersomeness, measured by the SBI (0-24), higher scores indicate more symptom bothersomeness.
- ≥30% improvement in leg pain score
- ≥50% improvement in leg pain score
- Global perceived change measured on a 7-point Likert scale (sciatica/back problem completely gone, much better, better, a little better, no change, a little worse, worse and much worse).
- Rescue medication consumption, measured by pill count, i.e. the number of Paracetamol pills not returned at the end of study. If the Paracetamol package is not returned, self-report data from the electronic diary will be used. Higher rescue consumption indicates more pain.
- Concomitant use of opioids, higher consumption indicate more pain
- Ability to work or study full time, measured by 3 nominal categories (unable, able, other)

We consider the secondary outcomes to have equal importance.

26.2 Calculations of outcomes

- The RMDQ-S is scored by summing up the number of items the patient checks.
- The SBI consists of four sciatica symptoms. Each symptom is rated 0-6 and a total bothersomeness score is obtained by summing up the ratings across the four symptoms

- The responder outcomes will be calculated as the change in leg pain scores between baseline and end of treatment, relative to baseline. Subjects with ≥ 30% reduction in leg pain intensity will be classified as a 30% responder, others as non-responders. A similar procedure will be used to identify 50% responders.
- Use of weak opioids will be quantified using a weighted score by dividing the total dose taken from day 0 to day 10 by its respective DDD. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults [3].
- Use of strong opioids will be quantified by the total dose converted into morphine milligram equivalents (MME) [4].

27 Analysis methods

27.1 Analysis of the primary outcome

The primary objective of the NIS trial is to estimate and test treatment differences in leg pain intensity at 10 days after commencement of Naproxen or placebo. Multiple measurements taken on the same patient will be correlated. This is accounted for in the analysis by a mixed effects model; either a linear mixed model (LMM) or a generalized linear mixed model (GLMM) depending on the distribution of the leg pain intensity. The model includes fixed effects for treatment, time (11 time points), the treatment-by-time interaction, and baseline measurements of leg pain plus age and gender. The primary result will be the treatment effect estimates over the period of treatment with 95% CI.

27.2 Analysis of secondary outcomes

- Back pain intensity will be analyzed using the same model used to analyze the primary outcome.
- Disability and sciatica bothersomeness will be analyzed using the same model used to analyze the primary outcome, but with 3 time points.
- Responder analyses, i.e. 30% and 50% improvement in leg pain intensity, will be performed using a mixed effects logistic regression model to obtain estimates of odds ratios (OR) and 95% CI. Based on the absolute risk reduction (ARR) between Naproxen and placebo we will calculate the numbers needed to treat (NNT) with 95% CI (NNT = 1/ARR).
- Rescue medication consumption and concomitant use of opioids during the treatment period will be analyzed using a suitable regression.
- Work/Study is an unordered categorical variable. The appropriate model is therefore a multinomial with repeated measurements and it will be analyzed using a GLMM.
- Global perceived change is an ordered categorical variable with repeated measurements and will be analyzed using a GLMM.

27.3 Adjustment for covariates

The statistical analyses of primary and secondary efficacy outcomes will be adjusted for baseline measures of the outcome where one is available [5]. The analysis of rescue medication consumption and use of concomitant opioids will be adjusted for baseline leg or back pain intensity depending on which is worse.

Study center (stratification variable) will not be included as covariate as we expect the majority of participants to be included at one center (Østfold). We will perform a sensitivity analysis with and without adjusting for center. Provided that a sufficient number of patients are included from at least 4 centers, these can be treated as additional random effects in the model.

27.4 Alternative methods

The analyses outlined in the previous sections should be considered as intentions in the sense that they rely on different assumptions. These assumptions may of course be challenged by the data, and the analyses will have to resort to other models. Alternatives may include Box-Cox analysis/transformation to achieve normality for non-normal continuous variables, bootstrapping random effects, and generalized additive mixed models (GAMM) as an alternative to the generalized linear mixed models.

27.5 Sensitivity analyses

We intend to assess the robustness of the results by

- Repeating the primary analysis in the PPP.
- Analyze the primary outcome using multiple imputation (MI) (see 28.3).
- Repeating the primary ITT analysis by including each of the following baseline variables as a covariate:
    - study centre (the stratification variable)
    - previous NSAID use (yes/no)
    - imaging findings

27.6 Subgroup analysis

We will not analyze subgroups.

28 Missing data

28.1 Measures to minimize the amount of missing data

- To facilitate simple access and timely responses patients receive daily text message reminders with a link to the electronic diary. A paper CRF is provided as back-up in case the eCRF is unavailable.
- To ensure clear and concise wording, and response alternatives, only validated patient reported outcomes, appropriate for sciatica, are used.
- To reduce unnecessary response burden the number of outcomes are limited.
- To ensure data completeness study staff checks the e-CRF at day 2 and day 5, and if necessary contacts the patient to clear up issues that may impair compliance.
- To preserve the ITT population data will be continued to be collected after withdrawal. Reasons for withdrawal are pre-specified.

28.2 Assessments of missing data

The number, timing, pattern, and known reasons for missing values will be assessed and summarized by treatment group and examined according to baseline characteristics. Missing data will be considered as either missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). If unexpected missing data patterns are found, sensitivity analyses in addition to those specified in 27.6, may be performed.

28.3 Statistical methods to handle missing data

The LMM and GLMM statistical models for analysis of the primary outcome and continuous secondary outcomes assume that missing data follow a missing at random (MAR) pattern, in which the probability of missingness may depend on other observed outcome values in the model, but are not related to the unobserved values of missing responses themselves. For outcomes not analyzed using likelihood-based methods (LMM and GLMM) missing data will be handled using multiple imputation (MI). MI will also be used in sensitivity analyses, see above (27.6).

MI under MAR or MCAR will initially be performed separately within each treatment arm. The models will include all variables in the analytic models plus the values of all baseline characteristics reported in Table 1. A total of 50 imputed data sets will be created. Pooled estimates will be calculated using Rubin's rules.

29 Additional analyses

29.1 Assessment of patient blinding.

At the end of treatment (day 10), or withdrawal, patients are asked to guess what treatment they have received. The response categories include (i) Naproxen, (ii) placebo and (iii) don't know. Descriptive data (2x3 table) will be presented, no statistical analyses will be performed.

29.2 Post hoc analyses

Any post-hoc exploratory analyses not identified in this SAP will be clearly identified as unplanned analyses. If unexpected missing data patterns are found in the data, we may conduct sensitivity analyses in addition to those predefined in this SAP.

30 Safety

An adverse event is an untoward medical occurrence after the administration of the first dose of a study drug through day 12 (±2).The number of non-serious and serious adverse events, and the proportion of subjects reporting ≥1 adverse event, will be summarized by treatment group and severity (mild / moderate / severe). We will also report the number and reasons for treatment discontinuation because of a treatment-related adverse event, as judged by the principal investigator. AEs will be summarized by frequencies and percentages and analyzed with chi-square tests.

31 Statistical software

Data manipulation, tables, figures, listings and analyses will be performed and documented using R, Stata and IBM-SPSS software.

32 Statistical summaries

For tables, sample sizes for each treatment group will be presented as totals in the column header (N=xxx), where appropriate. Sample sizes shown with summary statistics are the number (n) of patients with non-missing values. Summaries for categorical variables will include only categories that patients had a response in. Percentages corresponding to null categories (cells) will be suppressed. Summaries for continuous variables will include mean and SD. Other summaries (e.g. median, quartiles or range) will be used as appropriate. Percentages will be rounded and reported to a single decimal place. Summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). P-values <0.001 will be reported as <0.001.

32.1 Planned tables

Table 1. Baseline characteristics of participants by treatment group
Table 2. Intervention effect on primary and secondary outcomes
Table 3. Important and not important protocol deviations by treatment group
Table 4. Baseline concomitant medications by treatment group
Table 5. Response to blinding question at day 10
Table 6. Global perceived change (including all response categories) at day 5 and day 10 by treatment group
Table 7. Adverse events by treatment group and severity (mild / moderate / severe)
Table 8. Results of sensitivity analyses

32.2 Planned listings

List 1. Inclusion and exclusion criteria
List 2. Measurements and timing
List 3. Reasons for non-adherence to the intervention
List 4. Reasons for withdrawing participants from the study

32.3 Planned figures

Figure 1: CONSORT Diagram
Figure 2: Outcome scores over the 10-day treatment period, by treatment group. (Panel A; leg pain intensity, panel B; back pain intensity, panel C; disability)
Figure 3: Self-reported use of study medication over time, by treatment group
Figure 4: Proportions of subjects adherent to the intervention over time, by treatment group
Figure 5: Proportions of subjects compliant to follow-up over time, by treatment group

33 References

33.1 Data Handling Plan

The data handling plan was developed by the Clinical Trial Unit, Oslo University Hospital, and approved 27 oct 2017.

33.2 Statistical Master File

After database lock the clinical datasets will be delivered to the sponsor specified as SPSS files, one file per form as specified in the data handling plan. The data will be analyzed blinded to the randomization codes. Each participant will

be provided with a code A or B. When the analyses of the data are complete the investigators will be provided with which treatment (Naproxen or placebo) code A and B represents.

33.3 Procedures or documents to be adhered to

This SAP was developed based on Gamble et al; Guidelines for the Content of Statistical Analysis Plans in Clinical Trials [6]

The following documents were reviewed:

- Clinical Research Protocol for NSAIDs in sciatica (NIS) version no. 2.3
- e-CRF for NIS, Viedoc 4.37, 2017-11-01
- ICH Harmonized Tripartite Guideline on Statistical Principles for Clinical Trials [7]
- ICH Harmonized Tripartite Guideline on Estimands and Sensitivity Analysis in Clinical Trials [8]
- ICH Harmonized Tripartite Guideline on Structure and Content of Clinical Study Reports [9]
- EMA Guideline on Missing Data in Confirmatory Clinical Trials [10]

33.4 References

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6. Gamble, C., et al., *Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.* JAMA, 2017. **318**(23): p. 2337-2343.
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8. ICH. *E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials*. 2020 [cited 2020 3 Dec]; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf.
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SUGGESTED TABLE DESIGNS

Planned Table 1. Baseline characteristics

	Naproxen (N=)	Placebo (N=)
Age, mean (SD)		
Female sex, n (%)		
Body mass index, mean (SD)		
Smoking, yes, n (%)		
Education (years from first grade in primary school), median (IQR) or mean (SD)		
Employment status, n (%)		
Working or studying full time		
Not able to working or studying full time due to back problems		
Other		
Ever taken/used NSAIDs, n (%)		
Number of previous sciatica episodes, median (IQR) or mean (SD)		
Duration of current sciatica episode (weeks), median (IQR) or mean (SD)		
Previous back surgery, n (%)		
Treatment received for back problems (last month), n (%)		
Physiotherapy/chiropractic		
Other?		
Imaging findings*, n (%)		
Disc herniation		
Other†		
Imaging not performed		
Clinical examination findings, n (%)		
Sensory deficit,		
Motor deficit‡, n (%)		
Reflex deficit§, n (%)		
Pain on straight-leg raising maneuver, n (%)		
Leg pain intensity score (0-10), mean (SD)		
Back pain intensity score (0-10), mean (SD)		
Roland Morris Disability Questionnaire for Sciatica score (0-23), mean (SD)		
Sciatica Bothersomeness Index score (0-24), mean (SD)		
Concomitant use of pain medication, no (%)		
Any pain medication		
Weak opioids		
Strong opioids		

* Lumbar MRI or computed tomography (CT)
† No findings (n=), spondylosis (n=), etc.
‡ Reduced unilateral leg stand (Trendelenburg test), or toe or heel walking, or knee extension, or ankle flexion or extension, or big toe extension
§ Achilles or patellar

Planned Table 2. Intervention effects

	Naproxen (N=)	Placebo (N=)	
	Mean* or percentage (95% CI)	Mean* or percentage (95% CI)	Difference (95% CI)
Primary outcome			
Change in leg pain intensity			
Secondary outcomes			
Change in back pain intensity			
Change in disability			
Change in sciatica bothersomeness			
Percentage of participants with ≥30% improvement in leg pain intensity			
Percentage of participants with ≥50% improvement in leg pain intensity			
Likert score for global perception of change			
Percentage of participants unable to work or study full time due to back problems			
Rescue medication consumption †			
Concomitant use of weak opioids ‡			
Concomitant use of strong opioids §			

* Least square means

† Paracetamol tablets

‡ Quantified by defined daily dose (DDD)

§ Quantified by morphine milligram equivalents (MME)